DETAILED ACTION

This application 10/541,354 is a 371 of PCT/EP04/00030 filed on 01/05/2004, and claims benefits of foreign applications DE 103 00 023.2 filed on 01/03/ 2003; DE 103 10 160.8 filed on 03/07/2000; DE 103 36 642.3 08/10/2003; and DE 103 46 614.2 filed on 10/08/2003.

It is noted that the initial Election/Restrictions of instant application was mailed on 06/18/2008 and Non-Final office action was mailed on 12/22/2008. The Election/Restrictions mailed on 07/16/2009 was necessitated by claim amendments filed on 06/22/2009 because in the reply filed by Applicant on 06/22/2009 to Non-Final office action mailed on 12/22/2008, Applicant cancelled claims 1-91 and added new claims 92-101.

Election/Restriction

Applicant's confirmation of Applicant's initial election with traverse of Group II, claims 1 and 3, drawn to "use claim" that was interpreted as, for restriction purpose, a method of using the *translation product(s)* thereof one or several nucleic acid(s) in a process, whereby the process is selected from the group comprising angiogenesis, neovascularization, transmyocardial revascularization, wound healing, angiogenesis following wounding, epithelialization and healing of tooth and bone implants, whereby the nucleic acid(s) is/are one(s) that code(s) for high mobility group (HMG) proteins, including HMGB 1 or a part thereof, in the reply filed on 01/15/2010, which is in response to the Election of Species Requirement mailed July 16, 2009, is acknowledged. Applicant further elects the species HMGB1 for prosecution on the merits with traverse. Applicant states that claims 92-94, 97-98 and 100 to 101 filed on 06/22/2009 read on the elected invention.

The traversal filed on 01/15/2010 is on the ground(s) that there is no undue burden for the Examiner to search the full scope subject matter claimed in the present application, particularly with regard to each of the species set forth in the invention of Group II, and that there can be no undue burden to search and examine claim 99 with the invention of Group II, as a full search of the invention of Group II would encompass searching the subject matter of that claim.

This is not found persuasive because, as stated in the Restriction mailed on 07/16/2009, claim 99 is directed to the method according to claim 92, further comprising incubating said tissue or fragment thereof with a translation product derived from the VEGF gene or a fragment thereof. The translation product derived from the VEGF gene or a fragment thereof recited in claim 99 is not encompassed by elected Group II invention. Therefore, claim 99 had been assigned to a new group, Group XXVII (the Restriction requirement mailed on 06/18/2008 listed Group I-XXVI). The inventions recited in claim 92 and claim 99 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Applicant's claims encompass multiple inventions with multiple methods (methods of promoting angiogenesis requires HMGB1 protein, and methods of promoting angiogenesis requires both HMGB1 and VEGF protein), and do not have a special technical feature which link the inventions one to the other, and lack unity of invention. The common technical feature is methods of promoting angiogenesis comprising incubating a tissue with an HMGB1 protein. However, this common technical feature cannot be a special technical feature under PCT Rule 13.2 because the feature is shown in the prior art (See 103 rejection in this office action). The search for claim 99 of Group XXVII and the search for claim 92 of Group II is distinct one from each other and not co-

extensive and thereby presents search burdens on the examiner. However, it is further noted, that search burden is not germane to PCT lack of unity practice.

With regard to election of species, translation product HMGB1, translation product HMGB2, and translation product HMGB3 recite din claim 92 are different HMGB proteins belonging to HMGB family with distinct amino acid sequences, and different in structures and functions. Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a). As Applicant elected HMGB1 as elected species of the limitation "a translation product of a high mobility growth protein gene, or a fragment thereof" recited in claim 92, claim 95 reciting various HMGA proteins and claim 97 reciting "wherein one translation product is selected from the HMGA family" are directed on non-elected species. Claim 96 depends from claim 95, and claim 98 depends from claim 97.

Therefore, as discussed in two preceding paragraphs, claims 95-99 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

Claims 92-101 are pending. Claims 92-94, 100, and 101 are currently under examination to the extent of elected species HMGB1 as "a translation product of a high mobility growth protein gene".

The requirement is still deemed proper and is therefore made FINAL.

Priority

This application 10/541,354 is a 371 of PCT/EP04/00030 filed on 01/05/2004, and claims benefits of foreign applications DE 103 00 023.2 filed on 01/03/ 2003; DE 103 10 160.8 filed on 03/07/2000; DE 103 36 642.3 08/10/2003; and DE 103 46 614.2 filed on 10/08/2003.

The Examiner notes that Applicant cannot rely upon the foreign priority papers to overcome the rejection under 35 USC 102 (e) or 102 (a), when applicable, because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

The Examiner further notes that Applicant benefits priority one year before US filing date (filing date of PCT/EP04/00030 on 01/05/2004), but not one year before the earliest priority of foreign documents (DE 103 00 023.2 filed on 01/03/ 2003). In other words, a reference published before 01/05/2003 is considered as 102(b) art because it is published one year before 01/05/2004 (filing date of PCT/EP04/00030).

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Previous rejection of claims 1 and 3 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because the claims merely recites a use without any active,

positive steps delimiting how this use is actually practiced, is ***moot*** because the claims have been cancelled.

Claim Rejection - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

2. Previous rejection of claims 1 and 3 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101, is ***moot*** because the claims have been cancelled.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Previous rejection of claims 1 and 3 are rejected under 35 U.S.C. 102(e) as being anticipated by **Bianchi et al.** (US 2004/0136979, publication date 07/15/2004, filed on 03/16/2001), is ***moot*** because the claims have been cancelled.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. Claims 92-94, 100, and 101 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Andersson et al.** (Andersson et al., HMGB1 as a DNA-binding cytokine, *J Leukoc Biol.* 72(6):1084-91, 2002) in view of **Okamoto et al.** (Okamoto et al., Angiogenesis induced by advanced glycation end products and its prevention by cerivastatin, *FASEB J.* 16(14):1928-30, 2002), and **Kirkpatrick et al.** (Kirkpatrick et al., Tissue response and biomaterial integration: the efficacy of in vitro methods, *Biomol Eng.* 19(2-6):211-7, 2002).

Claim 92 is directed to a method of promoting angiogenesis in a tissue or part thereof, comprising incubating a tissue or part therefore with a translation product of a high mobility

growth protein gene, or a fragment thereof and, optionally, obtaining or recovering the tissue or an intermediate thereof.

Claims 93 and 94 further limits claim 92 by the limitation wherein the translation product is HMGB 1.

Claim 100 further limits claim 92 by the limitation wherein said tissue is an *in vitro* culture tissue.

Claim 101 further limits claim 100 by the limitation wherein said tissue is an explanted tissue.

Andersson et al. teaches that extracellular HMGB1 as a potent macrophage-activating factor, signaling via the receptor for advanced glycation end-products to induce inflammatory responses (See abstract, left column, page 0184, Andersson et al.). Andersson et al. teaches that HMGB1 is a specific and saturable ligand for RAGE binding with a higher affinity than the receptor's other known ligands, advanced glycation end products (AGEs). Andersson et al. teaches that HMGB1-induced intracellular signaling through RAGE can activate two different cascades, one involving the small GTPases Rac and Cdc42, leading to cytoskeletal reorganization, and a second that involves the Ras-mitogen-activated protein (MAP) kinase pathway and subsequent nuclear factor (NF)-κB nuclear translocation-mediating inflammation (See left column, page 1087, Andersson et al.). Andersson et al. teaches that there are two distinctly separate ways for HMGB1 to be secreted from a cell: HMGB1 can be passively released from the nuclei of necrotic or disintegrating, damaged cells or actively secreted from activated macrophages/monocytes or pituicytes, which does not involve cell death (See Figure 2, shown below, Andersson et al.).

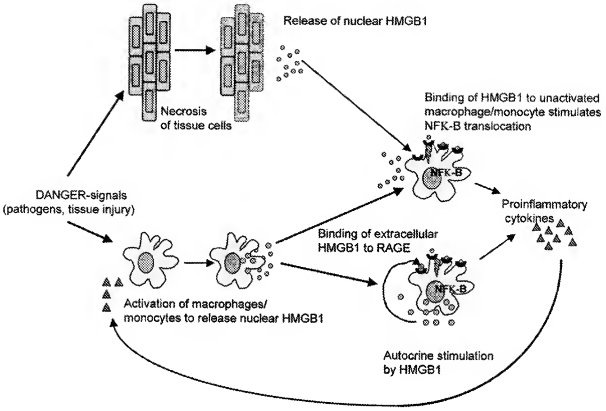

Figure 2. Schematic illustration of potential pathways for HMGB1 release leading to inflammatory responses. HMGB1 can be extracellularly released by passive secretion from any necrotic cell or by active secretion from activated macrophages/monocytes.

Andersson et al. does not explicitly teach **(i)** the effect of HMGB1 protein in promotion of angiogenesis recited in claims 92-94, and **(ii)** the limitation wherein said tissue or part thereof is an *in vitro tissue* recited in claim 100, and **(iii)** the limitation wherein said tissue is an explanted tissue recited in claim 101.

With regard to **(i)** the effect of HMGB1 protein in promotion of angiogenesis recited in claims 92-94, and **(ii)** the limitation wherein said tissue or part thereof is an *in vitro tissue*

recited in claim 100, **Okamoto et al.** teaches that when human skin microvascular endothelial cells (EC) were cultured with glycer-AGE or glycol-AGE, growth and tube formation of EC, the key steps of *angiogenesis*, were significantly stimulated. The AGE-induced growth stimulation was significantly enhanced in AGE receptor (RAGE)-overexpressed EC. Furthermore, AGE increased transcriptional activity of nuclear factor-κB (NF-κB) and activator protein-1 (AP-1) and then up-regulated mRNA levels of vascular endothelial growth factor (VEGF) and angiopoietin-2 (Ang-2) in EC. Okamoto et al. teaches that cerivastatin, a hydroxymethyl-glutaryl CoA reductase inhibitor; pyrrolidinedithiocarbamate; or curcumin was found to completely prevent the AGE-induced increase in NF-κB and AP-1 activity, VEGF mRNA up-regulation, and the resultant increase in DNA synthesis in microvascular EC (See abstract, Okamoto et al., 2002).

With regard to **(iii)** the limitation wherein said tissue is an explanted tissue recited in claim 101, **Kirkpatrick et al.** teaches that implantation involves tissue trauma, which evokes an inflammatory response, coupled to a wound healing reaction, involving angiogenesis, fibroblast activation and matrix remodeling. Kirkpatrick et al. teaches that three principal fields of research can yield useful data to understand these phenomena better: studies on explanted biomaterials, animal models and relevant *in vitro* techniques. Kirkpatrick et al. teaches the application of endothelial cell (EC) culture systems to study the effects of important tissue (e.g. pro-inflammatory cytokines, chemokines) and material (e.g. metal ions, particulate debris) factors on the regulation of the inflammatory and angiogenic response (See abstract, Kirkpatrick et al.).

Therefore, it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made to combine the teachings of Andersson et al. regarding HMGB1 is a

specific and saturable ligand for RAGE binding with a higher affinity than the receptor's other known ligands, advanced glycation end products (AGEs); HMGB1-induced intracellular signaling through RAGE can activate two different cascades, one involving the small GTPases Rac and Cdc42, leading to cytoskeletal reorganization, and a second that involves the Ras-mitogen-activated protein (MAP) kinase pathway and subsequent nuclear factor (NF)-κB nuclear translocation-mediating inflammation, with the teachings of (i) Okamoto et al. regarding activation of RAGE signaling pathway promotes angiogenesis in cultured human skin microvascular endothelial cells (EC), and the teachings of (ii) Kirkpatrick et al. regarding the application of endothelial cell (EC) culture systems to study the effects of important tissue (e.g. pro-inflammatory cytokines, chemokines) and material (e.g. metal ions, particulate debris) factors on the regulation of the inflammatory and angiogenic response in an explanted tissue, to arrive at the claimed methods of method of promoting angiogenesis in a tissue as recited in claims 92-94, 100, and 101 of instant application.

One of ordinary skill in the art would have been motivated to combine the teachings of Andersson et al. Okamoto et al. and Kirkpatrick et al. because (i) Andersson et al. teaches HMGB1 is a DNA-binding cytokine and a specific and saturable ligand for RAGE binding, and Andersson et al. proposes further investigation of relationship between vascular endothelial cells (EC), macrophage and HMGB1 (See left column, page 1090, Andersson et al.), (ii) Okamoto et al. teaches activation of RAGE signaling pathway promotes angiogenesis in cultured human skin microvascular endothelial cells (EC); and (iii) Kirkpatrick et al. teaches the application of endothelial cell (EC) culture systems to study the effects of important tissue (e.g. pro-

inflammatory cytokines, chemokines) and material factors on the regulation of the inflammatory and angiogenic response.

There would have been a reasonable expectation of success given (i) established interaction between HMGB1 and RAGE leading to transcriptional activation of NK-κB transcription factors via nuclear translocation mediated by RAGE signaling pathway, by the teachings of Andersson et al., (ii) successful demonstration of activation of RAGE signaling pathway promotes angiogenesis by activation of NK-κB transcription factors in cultured human skin microvascular endothelial cells (EC), by the teachings Okamoto et al. (See Figures 1-3), and (iii) successful demonstration of application of endothelial cell (EC) culture systems to study the effects of important tissue (e.g. pro-inflammatory cytokines, chemokines) and material factors on the regulation of the inflammatory and angiogenic response in an explanted tissue, by the teachings of Kirkpatrick et al. (See Figures 2 and 5).

Thus, the claimed invention as a whole was clearly *prima facie* obvious

The Examiner would like to direct Applicant's attention to recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.* that forecloses the argument that a **specific** teaching, suggestion, or motivation is an absolute requirement to support a finding of obviousness. See recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1936) (available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf). The Examiner notes that in the instant case, even in the absence of recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.,* the suggestion and motivation to combine Andersson et al. Okamoto et al. and Kirkpatrick et al. have been clearly set forth above in this office action.

It is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Conclusion

5. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/
Primary Examiner
Art Unit 1632